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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,675	02/12/2001	Nicholas C. Nicolaides	01107.00098	8276

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EXAMINER

AKHAVAN, RAMIN

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/780,675

Applicant(s)

NICOLAIDES ET AL.

Examiner

Ramin (Ray) Akhavan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6,7,16-18,26,27 and 71-73 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6,7,16-18,26-27 and 71-73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

An amendment to the claims, filed on 03/10/2004, is acknowledged. The claims pending are 1, 6-7, 16-18, 26-27 and 71-73. All objections and rejections not repeated herein are withdrawn. With respect to rejections that are maintained, Applicant's arguments will be addressed in the body of the rejections below. In addition there is a new ground for rejection (*Infra*, Double Patenting).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-7, 16-18, 26-27 and 71-73 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new rejection.

The claims are drawn to methods for making hypermutable bacterium by introducing into bacterium a polynucleotide encoding any dominant negative PMS2 mismatch repair protein or encoding any PMSR or PMS2L mismatch repair protein, whereby expression of such protein confers a dominant negative effect on mismatch repair resulting in hypermutable bacterium. In addition more particular claims are drawn to PMS2 from any source, where there is a truncation mutation at codon 134.

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The critical structural requirement of the invention is that any protein from the PMS2, PMSR and PMS2L family of proteins (or truncated versions of PMS2 at codon 134), when expressed in any bacterium, must interact with the host bacterial mismatch repair mechanism so as to exert a dominant negative effect resulting in a hypermutability. In other words, the claims are drawn to genera of mismatch repair proteins, i.e. PMS2, PMSR or PMS2L, with the requirement that a dominant negative effect is exerted through expression of any of said proteins when expressed.

The written description for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosures of relevant identifying characteristics, i.e. structure or physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus. Moreover, the written description requirement is grounded in the concept of predictability viz., structure to function correlation, with respect to different species within a genus. Put another way, the disclosure is sufficient when substitution of a disclosed species with an undisclosed species would result in a predictable outcome.

The specification teaches that expression of a human homologue to bacterial MutL – hPMSR3, in *E. Coli* causes hypermutability (Example 2) and two PMS2 truncation mutants from human and plant that exert a dominant negative effect when expressed in bacteria (Example 3).

In Remarks filed, 03/10/2004, Applicant contends that one of ordinary skill in the art would readily envisage all bacteria and all species within the family of claimed mismatch repair proteins that fall within the scope of the invention.

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More specifically, Applicant proffers that the instant invention is similar to an invention drawn to expression of proteins in any cell, where only a limited number of cells are disclosed. (Remarks, p. 8, ¶¶ 1-2). Applicant's comparison ignores the critical difference between production of a protein in a cell, versus expression of a protein in a cell with the aim to alter a specific mechanism in that cell (i.e. mismatch repair mechanism). Applicant's argument would be on point, if the only issue were whether the claimed family of mismatch repair proteins could be expressed in any bacterial cell. However, the invention requires more than mere expression, but rather, involves the expressed protein conferring a mechanistic change specific to mismatch repair. Therefore the disclosure for a particular species of bacterium would be inextricably linked to the species of mismatch repair protein being expressed, with the aim of altering the mismatch repair mechanism.

Applicant contends that a demonstration where dominant negative mismatch repair proteins from species as disparate as human and plant exert the desired effect, is enough to extrapolate the same effect from any PMSR, PMS2 and PMS2L protein. (Remarks, p. 9, ¶ 2). In addition, Applicant suggests that the fact that over expression of wild-type mismatch repair alleles from species including mouse, plants, yeast and human have been shown to induced a dominant negative effect in bacteria, evidences a strong conservation of the components of the mismatch repair pathway among a broad array of species. (Id. at ¶ 3).

Notably, there are examples of highly conserved species of mismatch repair proteins that behave in an unexpected fashion, as compared to that which Applicant contends. For example, even within bacterial species, it has been shown that expression of hexA, a *Streptococcus pneumoniae* homologue of *E. Coli* MutS, causes hypermutability in *E. coli*, but significantly,

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expression of hexB, a homologue of MutL, does not. (*See* Prudhomme et al. J. Bacteriology, 1991; 173:7196-203; cited in IDS).

Additional evidence shows that members within the highly conserved human family of mismatch repair proteins may not be involved in mismatch repair at all. For example, highly conserved species within the family of PMS2L proteins do not interact with a major DNA mismatch repair protein – hMLH1. (*See* Kondo et al. J. Biochem. 1999; 125: 818-825; Abstract). The hMLH1, like PMS2, is a mutL homologue, which forms a heterodimer with PMS2. (*Id.* at p. 824, col. 1, ¶ 2). This would suggest to one of ordinary skill in the art that there is a level of unpredictability with respect to even highly conserved species of mismatch repair proteins. Indeed, as is acknowledged in the art, even highly conserved mismatch repair proteins may have completely different roles in a cell, rather than involvement in mismatch repair mechanisms. (*Id.* at col. 2, last ¶). Given that highly conserved species may not be involved in the mismatch repair mechanism, then it would logically follow that truncated versions of the same, i.e. at codon 134, would also not necessarily be involved in the prescribed function.

Therefore, it would be evident to one of ordinary skill in the art that applicant is not in possession of the claimed invention. Given the enormous breadth of the mismatch repair proteins encompassed by the rejected claims (i.e. PMS2, PMSR, PMS2L and PMS2-134), and given the limited description from the instant specification of such in light of the what is known in the art, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of mismatch repair proteins. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results

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obtained from other species (*Supra*, Prudhomme and Kondo). Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16, 17 and 71 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-3 and 36 of copending Application No. 09/912,697. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows:

Instant claims 16, 17 and 71 are drawn to a method of making hypermutable bacterium through expression of PMS2-134, human PMS2-134 and plant PMS2-134.

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Reference claims 1-3, 36 are drawn to a method of producing antibiotic resistant bacteria comprising over expressing mismatch protein in bacteria thereby making the bacteria hypermutable. The reference claims are narrower in scope because the bacterial hypermutability is further selected via contacting the bacterium with an antibiotic. Put another way, the hypermutability is selected for, via a single phenotypic trait (i.e. antibiotic resistance). Otherwise, both the reference and instant claims are drawn to producing hypermutable bacterium through expression of PMS2-134. In each case bacteria are made hypermutable through expression of PMS2-134. The reference claims anticipate thus necessarily make obvious instant claims.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.


Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


GERRY LEFFERS
PRIMARY EXAMINER